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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,477	10/04/2001	Attila T. Lorincz	2629-4005US4	2780

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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/970,477	Applicant(s) LORINCZ ET AL.	
	Examiner Diana B. Johannsen	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The following papers have been entered: the Preliminary Amendment filed October 4, 2001 (paper no. 3), and the paper and computer readable forms of the Sequence Listing filed February 27, 2002. It is also noted that the amendment to the first line of the specification contained in the transmittal letter of paper no. 7 (filed October 4, 2001) has been entered.

Priority

2. The instant application is a continuation of U.S. application no. 09/210,168, filed December 11, 1998, and claims the benefit of U.S. provisional application nos. 60/082,167, filed April 17, 1998, 60/070,486, filed January 5, 1998, and 60/069,426, filed December 12, 1997. As the '168 application issued on March 12, 2002, the first line of the specification should be amended so as to indicate that U.S. application no. 09/210,168 is "now U.S. Patent No. 6,355,424."

Information Disclosure Statement

3. The information disclosure statement filed October 4, 2001, paper no. 8, fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. Accordingly, foreign patents EP0502994B1 and DE4445769CL have not been considered.

Specification

4. It is noted that page 5 of the specification includes a non-initialed, non-dated handwritten correction of a typographical error in a SEQ ID NO. This typographical error was corrected in parent application 09/210,168 in an amendment filed June 5, 2000, which amendment is referenced in the declaration filed with the instant application. As the handwritten change to the specification corrects an obvious typographical error (i.e., as it is clear that the sequence in Figure 3 corresponds to SEQ ID NO: 1 and should be properly identified as such), the examiner has corrected the obvious error and initialed and dated the correction in order to ensure proper entry thereof.

5. The use of the trademarks CDP-Star® (p. 14), PreservCyt® (p. 18), and CytoRich™ (p. 18) has been noted in this application. The trademarks should be capitalized wherever they appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 8-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Claims 8, 10, and 11 are drawn to methods of "diagnosing risk of HPV-induced neoplasia by detecting HPV-induced cell transformation in a patient infected with HPV" (claim 8), methods of "diagnosing stage of HPV-induced disease in a patient infected with HPV" (claim 10), and methods of "diagnosing HPV-induced cancer in a patient infected with HPV" (claim 11). In these methods, the ratio of E6 and/or E7 mRNA level to L1 and/or L2 and/or E2 mRNA level is determined, and a ratio of greater than 2 is indicative of "HPV-induced cell transformation and risk of neoplasia" (claim 8) or "early stage HPV-induced disease" (claim 10), while a ratio of greater than 4 is indicative of "HPV-induced cancer" (claim 11). Claims 9 and 12 are drawn to methods "of diagnosing the onset of HPV-induced disease in a patient infected with HPV" (claim 9) and methods "of diagnosing the risk or onset of HPV-induced cancer in a patient

infected with HPV" (claim 12). In these methods, the ratio of group I mRNA level to group II and/or group III mRNA level is determined, and a ratio of greater than 2 is indicative of "HPV-induced neoplastic onset" (claim 9), while a ratio of greater than 4 is indicative of "high risk or onset of HPV-induced cancer" (claim 12). The specification indicates that group I genes include E6, E7, and E6 + E7, that group II genes include L1, L2, E4, and combinations thereof, and that group III includes E1, E2, E5, and combinations thereof (specification p. 10).

The specification exemplifies quantitation of HPV mRNA in different cultured cell lines (Example 1-2, Example 4). Cell lines examined include HaCaT cells, SiHa cells, and W12 cells. The specification teaches that HaCaT cells are an "immortalized human keratinocyte cell line" comprising approximately 1 episomal copy of HPV16 for every 40 cells, and states that "These cells are considered a representative of early stage infection or CIN I (cervical intraepithelial neoplasia)" (p. 22-23). The specification teaches that SiHa cells are a "human cancer cell line" containing "1-2 copies of HPV16 integrated into the genome", and states that "These cells are considered to represent cancer" (p. 22-23). The specification teaches that W12 cells are a "non-tumorigenic human cervical keratinocyte cell line" that "contain approximately 100 copies of episomal HPV16 DNA and represent pre-malignant, immortalized cells or CIN II or CIN III" (p. 22-23).

The teachings of the specification show that the HPV16 (E6+E7)/L1 mRNA ratio is 0.68 for "early stage infection" HaCaT cells, 4.00 for "pre-malignant, immortalized" W12 cells, and "infinitely large" for "malignant" SiHa cells (p. 24, Table 2). Thus, based

on the teachings of the specification, it appears that one of skill in the art could distinguish these three cell culture models of infection from one another by determining the HPV16 (E6+E7)/L1 gene transcript ratio. While the specification indicates that other ratios of HPV16 gene transcripts were measured and calculated for W12 and SiHa cells, no other data is presented for HaCaT cells (Table 2). Thus, based on the data presented by Applicant, it is not known what HPV16 mRNA ratios exist in HaCaT cells for transcript combinations other than (E6+E7)/L1. However, with respect to W12 and SiHa cells, Applicant further demonstrates that these two cell types have different HPV16 mRNA ratios for 5 other transcript combinations (see Table 2).

It is unpredictable as to whether one of skill in the art could practice the claimed invention. While the instant claims are directed to methods of, e.g., diagnosing cancer, cancer risk, or neoplastic onset in a patient, the specification does not provide evidence that the HPV gene transcript ratios set forth in the claims are associated with transformation, cancer, disease stage, etc., in a patient. The data presented in the specification are limited to HPV16 transcript ratios in different types of cultured cell models, as discussed above. It is also noted that Applicants have not provided any type of declaratory evidence that establishes the validity of the various types of cultured cells employed in the specification as disease models, as was provided in parent application 09/210,168. Accordingly, in view of the lack of guidance provided in the specification, one must rely on the teachings of the prior art to provide further guidance and enablement of the methods of claims 8-12. The prior art is silent with respect to a correlation or correspondence between HPV gene transcript ratios measured in the 3

particular cell culture models employed by applicants and ratios measured in, e.g., different types of tissues samples taken from patients. Accordingly, neither the specification nor the art provide evidence that ratios measured in the 3 cell types employed by applicants are predictive of results that would be obtained in assaying patient tissues. The prior art as exemplified by Stoler et al (Human Pathology 23(2):117-128 [2/1992]) does suggest that expression of HPV E6 and E7 genes is elevated in some types of cancers (see entire reference). For example, Stoler et al demonstrate that, in high-grade squamous intraepithelial lesions associated with HPV-16, "signals from the E6-E7 ORFs were equal to or higher than from those from the E4-E5 region", whereas in low-grade squamous intraepithelial lesions, "Probes for transcripts spanning the E4-E5 ORFs yielded the most intense signals" (p. 119). However, the claimed invention is limited to the detection of particular ratios of mRNA levels to accomplish diagnosis, and the prior art, as exemplified by Stoler et al, does not provide evidence that detection of the particular transcript ratios required by the instant claims would allow diagnosis in a patient of cancer, cancer risk, cancer stage, neoplastic onset, etc. Stoler et al also teach that the types and quantities of HPV transcripts expressed in patients will vary depending on cancer type, HPV type, and cell/tissue location (p. 119-120). Stoler et al further teach that HPV types 6 and 11, 16, and 18 are associated with different disease types (p. 117), and it is well known to those of skill in the art that different HPV types are associated with different disease types and cause diseases of varying severity. Thus, neither the specification nor the teachings of the prior art establish a correspondence or correlation between the particular ratios of

HPV transcripts recited in the instant claims and "HPV-induced cell transformation" or risk for/onset of/stage of HPV-induced cancer in a patient. As it is unknown as to whether such a correspondence or correlation exists, it is unpredictable as to whether any quantity of experimentation would be sufficient to allow one of skill in the art to use the claimed invention. Further, based on the teachings of the specification and of the prior art, it is not only unpredictable as to whether the transcript ratios observed by Applicants in cultured cells might correlate with ratios in a patient, but to what types of HPVs and what types of cancers said ratios might be relevant. The data provided in the specification is limited to HPV16, and the prior art as exemplified by Stoler et al establishes that different HPV types are associated with different disease types. Accordingly, even if it were to be established that, e.g., the cultured cell models employed by Applicants in assaying HPV16 were valid models of HPV16-associated disease in patients, it is unpredictable, based on the guidance provided in the specification and in the art, as to whether detection of such ratios in patients would be useful in diagnosis of disease caused by other HPV types. In view of the lack of guidance in the specification and in the prior art with respect to diagnosis and/or monitoring of cancer in a patient by determination of the HPV gene transcript ratios of the claims, including HPV16 gene transcript ratios, it would require undue experimentation to use the claimed invention.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 8-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, respectively, of U.S. Patent No. 6,355,424B1. An obviousness type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). In the instant case, although the conflicting claims are not identical,

they are not patentably distinct from each other because claims 8-12 of the instant application are generic to all that is recited in claims 1-5, respectively, of the '424 patent. That is, claims 1-5 of the '424 patent fall entirely within the scope of claims 8-12, respectively, or, in other words, claims 8-12 are anticipated by claims 1-5, respectively. Specifically, instant claims 8-12 are generic to any type of HPV, including HPV16, the species that is recited in claims 1-5 of the '424 patent. Thus, claims 1-5 of the '424 patent anticipate instant claims 8-12, respectively.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
February 10, 2003